MALARIA INFECTION AS IT OCCURS IN LATE PREGNANCY; ITS RELATIONSHIP TO LABOUR AND EARLY INFANCY

BY

D. B. BLACKLOCK

AND

R. M. GORDON

(*From the Sir Alfred Lewis Jones Research Laboratory, Freetown, Sierra Leone*)

(*Received for publication* 13 *July*, 1925)

PLATE VI

I. INTRODUCTION

In a previous paper (1925) we published an account of the malaria incidence in a series of twenty-six placentas of native women in Freetown. The investigation of placental malaria has been continued on all material available since then, so as to eliminate seasonable variations, and the records now cover a period of a complete year, i.e., from July, 1924, to July, 1925. Examinations have been made not only of films of the placental blood and of the peripheral blood of the mother at and about the time of labour, but also of cord and peripheral blood films of the children born of mothers with infected placentas. A small amount of material has been obtained from post mortem examination of children born dead or who died within a period of seven days. For purposes of comparison certain figures of the infection rate of the adult male population have been introduced.

The distribution of parasites in infected placentas has been studied with a view to discovering whether the whole placenta is equally infected or whether there is special concentration of the parasites in any particular areas.

Evidence of the transmission of parasites from the placenta to the child has again been sought. Although evidence of such transmission of parasites has never once been obtained throughout the whole series, yet there are certain facts which strongly suggest that the presence of malaria in the placenta is frequently associated with abnormal labour, that the death-rate among children born of mothers with infected placentas is unusually high, and that the

blood of the child is deleteriously affected by the parasitic invasion of the placenta. Little material from cases of abortion was available and what was obtained was not usually suitable for examination. It is not possible, therefore, to adduce any facts to show whether malaria is an important factor in the causation of abortion in Freetown or not. This is an aspect of the case which clearly requires attention, but until greater facilities for obtaining material are made it is not possible to advance much in this direction.

In our previous paper, we discussed the view held by some observers that new-born children of infected mothers possess a temporary and partial tolerance as regards malaria, so that a new-born child, although congenitally infected, does not present parasites in the peripheral blood at birth nor until after the lapse of a certain time. We argued that there was no direct evidence of the existence of such a partial tolerance on the part of the child, and that there was evidence against its existence at least in some cases, i.e., where authentic congenital malaria has been demonstrated. We noted, however, that of 41 children of one month or under, only one, a child between three and four weeks old, had parasites in the peripheral blood. In this present series it will again be seen that children under one month rarely show parasites in the peripheral circulation. This freedom from parasites in the peripheral blood may be due to freedom of the child from infection. If this is so, it may merely result from the fact that, for some unexplained reason, children up to a week or two old are little exposed to the bites of infected anophelines. On the other hand, it would be compatible with either a temporary general immunity, i.e., a condition during the existence of which the child is totally incapable of developing infection anywhere, or a condition of local immunity with partial tolerance, i.e., a condition in which the child is in fact infected, but in which the infection does not appear equally distributed throughout the body, but only in certain parts, of which the peripheral circulation is not one. That such local infections do occur in adult women, and, moreover, that they can very frequently exist without the production of obvious constitutional symptoms, we are able to prove conclusively from the present series.

We shall show that of 150 parturient native women, aged 15 to 42, examined during the period of twelve months, 55 proved to be

infected with *P. falciparum*. Of those infected, however, only 10 showed infection of both peripheral and placenta blood. In the remaining 45 only the placenta was infected.

It must be concluded, therefore, either that in these latter cases the parasites remain localised in the placenta, and never leave it, or else that if they do leave the placenta on their way to the peripheral blood via the vena cava, they are rapidly destroyed ; for it seems impossible to explain merely on the ground of dilution, the non-appearance of parasites in films from the peripheral circulation, when we consider that the placenta is a highly vascular organ, that it represents some $\frac{1}{120}$th of the total body weight and that of the maternal erythrocytes which it contains as many as 65 per cent. may be infected, as was shown by us previously (1925). See Plate VI, fig. 1.

It seems not only legitimate but necessary to believe that in pregnant native women infected with malaria, there are certain portions of the circulatory system which are immune from infection ; while at the same time, in the same individuals, other portions, far from being immune, exhibit massive infection, accompanied by active sporulation. If we admit a local immunity in the case of the mother, it must be admitted that a similar condition may exist in the child. Although in no case in a child born of a mother with placenta infected were parasites found either in the cord, peripheral blood, or in such organ smears as were available, we are not in a position to deny the possibility of malaria parasites establishing themselves in the internal organs of the child although not appearing in its peripheral blood. We can say, however, that such a condition, while it would be in accordance with the idea of the existence of local immunity in one portion of the child's circulation, namely, the peripheral blood, would equally imply the absence of such an immunity in another portion, namely, the umbilical cord. This question will be referred to again in discussing the age incidence of malaria infection in the children, and the fact that in a few cases of children born dead or who died immediately after birth, there was found in smears made from the internal organs, pigment which could not be distinguished from malaria pigment.

Before proceeding to a detailed account of the facts obtained, it may be noted as somewhat extraordinary that since the observa-

tions made on placental infection by the Greek observers Pezopoulos and Cardamatis (1907), little attention has been given to the discrepancy which appears to exist between the infection rate of males and females as judged by the peripheral blood rate of the former and the placental blood rate of the latter; nor, in our opinion, has sufficient attention been attached to this method of diagnosing malaria in the case of parturient women whose peripheral blood has yielded no evidence of it.

II. EXAMINATION OF THE PERIPHERAL BLOOD

A. Of mothers.

Thin film preparations of blood were made from the peripheral blood of 173 mothers at the time of labour; in addition to thin films, thick films were also examined in 71 of these cases. The number of cases in which malarial infection was diagnosed by examination of the peripheral blood was 12, of which 9 had parasites of *P. falciparum*, and 3 pigmented leucocytes only; it is noteworthy that in no case were gametes found, although in 5 of the 9 positive parasitic cases, one or more thick films were also examined.

Seasonal incidence of infection in the peripheral blood of mothers.

The number of mothers examined by films of the peripheral blood varied from 5 to 24 in a month; the total number examined and the approximate percentage found positive in each month are shown in Table I.

TABLE I.

Showing monthly total of mothers examined and percentage positive.

	Total	Percentage positive		Total	Percentage positive
July	8	25	January	17	6
August	5	20	February ...	5	0
September ...	10	10	March	7	0
October	16	0	April	27	7
November... ...	24	8	May	25	4
December ...	13	8	June	16	13

B. Of non-parturient women.

Of 43 women of the age of 16 and upwards, all, however, examined by means of thick film preparations from the peripheral blood, three had parasites. One of these was a *Plasmodium vivax* infection, the other two were *P. falciparum* infections, and in one of the latter crescents were present.

C. Of Adult males.

In a series of 150 males of the age of 16 and upwards, all examined by the thick film method, three had trophozoites of *P. falciparum* in the peripheral blood ; in no case were crescents found.

D. Of children.

Each one of a series of 809 children of all ages up to two years and a half was examined, on its first appearance, by thin film preparations of the peripheral blood ; an additional examination was made at the same time in the case of 100 of these children by the thick film method. Of the 809 children, 169, i.e., 20.9 per cent. had parasites in the peripheral blood ; *P. falciparum* occurred alone in 149 cases, *P. malariae* alone in 12 cases, and *P. vivax* alone in 2 cases ; mixed infection of *P. falciparum* and *P. vivax* occurred in 2 cases, of *P. falciparum* and *P. malariae* in 2 cases, and of *P. falciparum*, *P. malariae*, and *P. vivax* in 1 case. One case diagnosed by pigment alone cannot be classified. *P. falciparum* infection was found therefore in 19.0 per cent. of the 809 cases examined. Crescents were present in 23 cases, i.e., 14.9 per cent. of the 154 *P. falciparum* cases; this percentage is low, as in cases in which trophozoites were found at once, the examination was not continued to the time limit prearranged.

Seasonal incidence of malaria in the peripheral blood of 809 children up to 2½ years.

The monthly total number of new children examined by films of the peripheral blood varied from 36 to 104 ; the total examined and the percentage found positive in each month are shown in Table II.

TABLE II.

Showing monthly total of new cases examined and percentage positive.

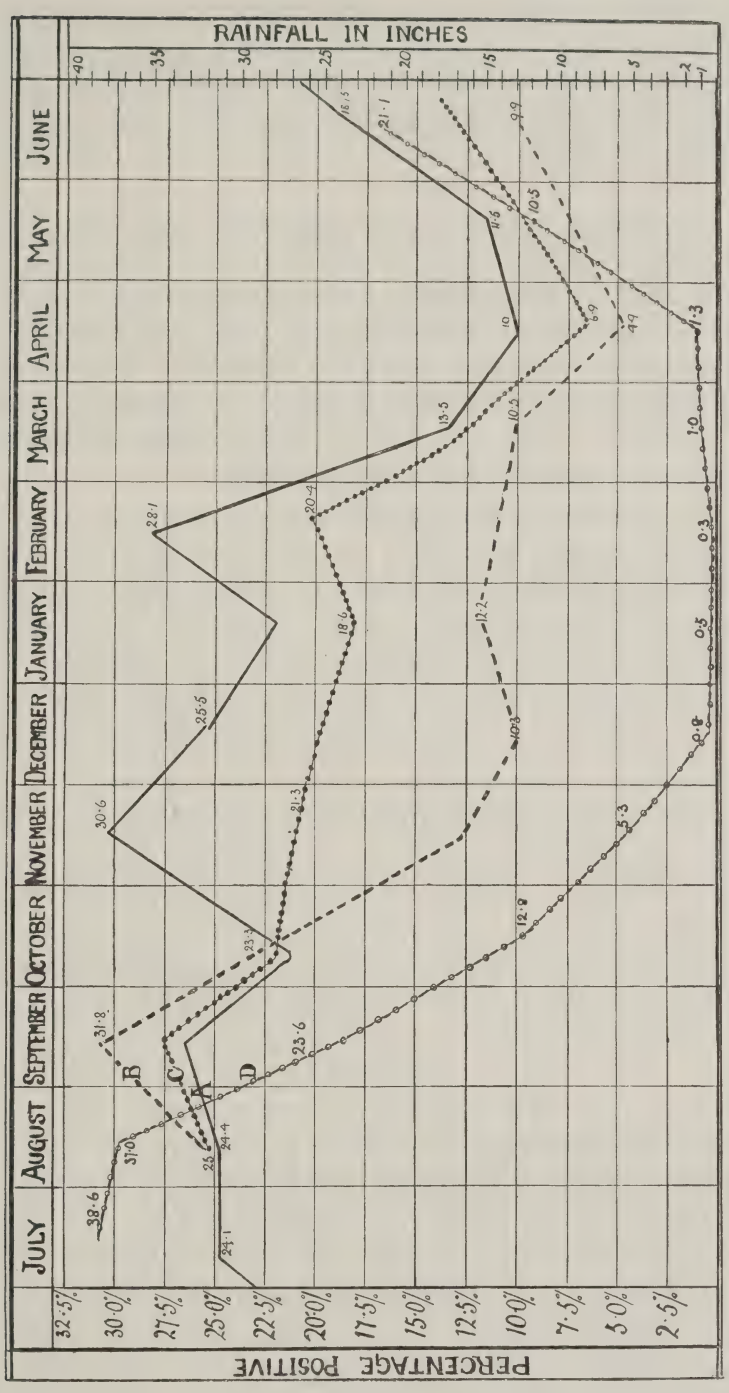
Month ...	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April	May	June
Total ...	62	78	93	60	36	51	77	57	104	40	87	64
Per Cent. positive...	24·1	24·4	26·8	21·7	30·6	25·5	22·1	28·1	13·5	10·0	17·2	18·7

Each case on its first appearance is classified here as new; on any subsequent appearance, therefore, it is classified as old, and the parasitic findings require separate record, as is shewn in the graph given below.

The number found positive among new cases in each month is expressed in Graph I A as a percentage of the total new cases appearing for examination for that month. The number of old cases found positive for the first time in each month is expressed in Graph I B as a percentage of the corrected total of old cases seen in that month. The corrected total of old cases is arrived at by excluding all cases which had previously been found positive. The numbers found positive in the above two categories are added together and expressed in Graph I C as a percentage of the total cases, i.e., new cases plus corrected old cases, appearing for examination in each month. The rainfall in inches in an average year is shown in Graph I D.

Table II and Graph I A, which give the same information, represent the results of a single examination; Graph I B represents the results of at least two, and it may be numerous examinations and includes all cases which, negative on first examination, proved positive at a later time; the resultant curve of the summation of the positives in A and B shown in Graph I C gives a more accurate impression of the seasonal incidence of malaria in the children than does A alone or B alone.

It is seen that the form of curve C which we regard as yielding the most reliable information on the question of seasonal incidence in children, presents a fairly definite relationship to the rainfall curve. The relationship is such as to show that soon after the commencement of the rains the malaria incidence rises. If we compare the peripheral



GRAPH I.

Showing seasonal incidence of Malaria and average rainfall in inches.

blood of children with the placentas of mothers (Section IV, Table V) we see that in the latter a rise occurs antecedent to the rains and before the rise in the children's infection. This suggests that the placental rise represents a seasonal relapse, while that of the children represents a seasonal infection.

III. EXAMINATION OF BLOOD FROM THE UMBILICAL CORD

Thin films of blood from a vessel in the umbilical cord were examined in 162 umbilical cords. In no cord was malaria infection found, in spite of the fact mentioned below that the examination of 155 of the placentas belonging to the cords revealed 59, i.e., 38 per cent. positive ; further, in spite of careful search, no pigmented leucocyte was ever found in the cord blood.

Maternal leucocytes in the foetal circulation.

It is stated that leucocytes can penetrate from the maternal into the foetal circulation ; this statement is based upon the relative numbers of leucocytes found in the umbilical arteries and vein. It has been found that the umbilical vein blood contains per volume a greater number of leucocytes than the umbilical arterial blood. This passage of leucocytes presumably occurs through the walls of the villi and is a matter which requires further investigation where placental infection with malaria occurs. It may not be justifiable to argue that where leucocytes can pass through, erythrocytes can also pass through ; still less is it justifiable to assume that infected erythrocytes can pass ; for it was observed by Marchiafava and Bignami (1894) that in capillary apoplexies almost all the extravasated red blood-corpuscles were without parasites, while the cerebral vessels contained immense numbers of red blood-corpuscles having parasites in them. It is, however, important to note that in these heavily infected placentas it is by no means rare to find leucocytes which contain within them parasites. These parasites may be of any size up to forms which are segmented and appear ready to rupture. It is not possible to say whether leucocytes containing such parasites are capable of penetrating from the maternal to the foetal circulation, nor is it possible to say whether such parasites, if liberated in the child's circulation, could infect it. All that can be said is that certain of these parasites contained in leucocytes were undoubtedly alive at the time of examination as evidenced by their movements visible

by the dark ground illumination method. These parasites containing leucocytes are, comparatively speaking, rare, and it is unlikely that even if they penetrated into the child's circulation, they would come under observation. In a number of placentas examined the majority of the leucocytes contained pigment (see Plate VI, fig. 2).

If the difference noted by some observers between the total leucocytes present in the umbilical cord vein and arteries is, as stated by Gray (1923), due to the penetration of the maternal leucocytes into the foetal circulation, it is difficult to account for the fact that in spite of the most careful examination we failed to find such pigmented leucocytes in either the cord or the peripheral blood of the child.

In the endeavour to ascertain whether the condition of the arterial and venous cord blood, as regards the proportion of leucocytes present, is as stated, we have in one case made careful enumeration of the leucocytes present in films of each. The result showed that such difference as existed between the leucocyte content of the venous and the arterial cord blood was negligible, but showed a slight preponderance of leucocytes in the arterial blood, in the proportion of arterial 187 and venous 170 to 50,000 erythrocytes.

IV. EXAMINATION OF BLOOD FROM THE PLACENTA

Of 155 placentas of native women examined for malaria 59 were found to be positive, that is 38.0 per cent.

The results of the different blood examinations obtained so far are set out in tabular form arranged according to the ascending percentage of parasitic positives.

Table III.

Showing the parasitic findings of various groups.

	Blood films of	162 Umbilical cords	150 Adult males (peripheral blood)	43 Non-parturient women (peripheral blood)	173 Mothers (peripheral blood)	809 Children (peripheral blood)	150 Mothers' placental blood	155 Placentas
Percentage having	Parasites ...	0·0	2·0	7	6·9	20·9	36·6	38·0
	Crescents ...	0·0	0·0	2·3	0·0	2·8	0·0	0·0

It is interesting to compare the above placental figures with those given in Table IV taken from Clark (1915), which shows the distribution of placental infection among different races in his series of 400 labours.

Table IV.

400 Routine cases of labour.

Race of the women examined	No. examined of each race	No. of positive identifications of malaria	Per cent. of positive cases
North Americans (white)	118	0	0·0
Latin Americans (mestizo) ...	92	3	3·26 +
Europeans (white)	17	1	5·88 +
West Indian Negroes	173	15	8·67 +
Total	400	19	4·75

It is seen that Clark's percentage of positive mothers is low as compared with ours, 4·75 per cent. as compared with 36·6 per cent. A partial explanation of this fact is obtainable from consideration of the groups forming his total. Thus the 118 North Americans (white) give a percentage infected figure of 0·0, whereas the 173 West Indian negroes give the highest figure a percentage infected of 8.67. The difference of incidence is attributed by Clark to the higher hygienic plane of the North Americans, to the greater exposure to infection of the West Indian Negroes on account of their residential surroundings and their much lower hygienic and economic standard. Even taking the figure for West Indian negresses alone, however, the infection rate, i.e., 8·67 per cent. does not approach that seen in West African native women in Freetown, i.e., 36.6 per cent. If placental findings are taken as a criterion of malarial infection, it appears that the West African native women in Freetown are more than four times as frequently infected as the West Indian negresses dealt with by Clark.

Seasonal incidence of infection of the placenta.

The number of mothers whose placenta was examined by blood films varied from 6 to 24 monthly during the year. The total

number examined and the percentage found positive in each month are shown in Table V.

TABLE V.

Showing monthly total of mothers examined and the percentage found positive.

	Total	Percentage positive		Total	Percentage positive
July...	8	62	January	18	39
August	6	33	February	7	43
September	12	42	March	11	18
October	16	19	April	11	18
November	24	38	May	15	53
December	13	31	June	9	56

Type of infection in the placental blood.

Without exception all the cases found positive in the placenta were infected with *P. falciparum ;* in one case a few parasites which resembled quartan were also found. In spite of prolonged examination of the placental films, no crescents were ever found in the placental blood. In writing the account of our first series of twenty-six placentas we drew attention to the absence of crescents in the placental blood, and also in the peripheral blood of such cases as showed infection there. We have obtained no evidence from this larger series that crescents are being formed elsewhere in these infected individuals, as no crescents have been found in any of them in the peripheral blood during, or immediately after, labour. If post-mortem material had been available it might have been possible to determine whether any crescents were present in internal organs. Blacklock (1921) produced evidence from a case of indigenous infection with *P. falciparum* in England that the bone marrow was the most suitable site for the development of crescents, a site which had previously been stated to be favourable by Marchiafava and Bignami and various other observers.

These cases, then, although the infection in the placenta is often very intense, are not producing crescents in this site. Nor does it appear probable that the parasites are migrating from the placenta

to develop elsewhere into crescents, because we do not find crescents in the peripheral blood. The failure of sexual forms to reach the peripheral blood must inevitably result in failure of the parasite to complete its development even when susceptible anophelines bite such women. The rare possibility of parasites of the schizogony cycle being transmitted congenitally to the child must be taken into consideration ; this would doubtless result in the formation later of gametes in the child, and so in a circuitous manner the stages infective for the mosquito would become available. In the meantime we have the fact, proved by abundant evidence, that the mere proliferation of *P. falciparum* on a colossal scale in one organ at least of native adult women does not result in the production of crescents in that organ, nor does it result in their appearance in the peripheral blood.

The anatomy and circulation of the placenta.

Before discussing the distribution of malaria parasites in the placenta, it is necessary to make same reference to the placental circulation. According to the descriptions and diagrammatic representations of the placenta and its circulation contained in many text books of anatomy, the condition is somewhat as shown in the left hand side of diagram No. 1. The arteries and vein of the child are carried from the umbilical cord, and pass subjacent to the amnion into the chorion ; the vessels are carried into the villous processes of the chorion ; the villi lie in the intervillous space and are bathed in maternal blood. As, however, the villi are covered by two layers of trophoblast, the cytotrophoblast layer next the chorionic process and the syncytiotrophoblast layer in contact with the maternal blood, the latter does not come directly in contact with the foetal blood vessels.

The maternal blood gains access to and leaves the intervillous space by arteries and veins which pass through the stratum spongiosum and the basal plate which represents the remains of the stratum compactum. The arteries as they enter the basal plate lose their muscular coat and they and the veins after this point consist of sinuous channels lined only by endothelium ; these channels open into the intervillous space, and at this point they lose their endothelial covering. The intervillous space is lined throughout by the syncytiotrophoblast layer. Therefore the walls of the

intervillous space and the villi which project into it are covered by the same lining structure.

The right-hand half of the figure represents the separated placenta ; according to Gray and others this separation occurs through the stratum spongiosum. On the right half of the diagram have been shown the areas in which infected and uninfected red blood

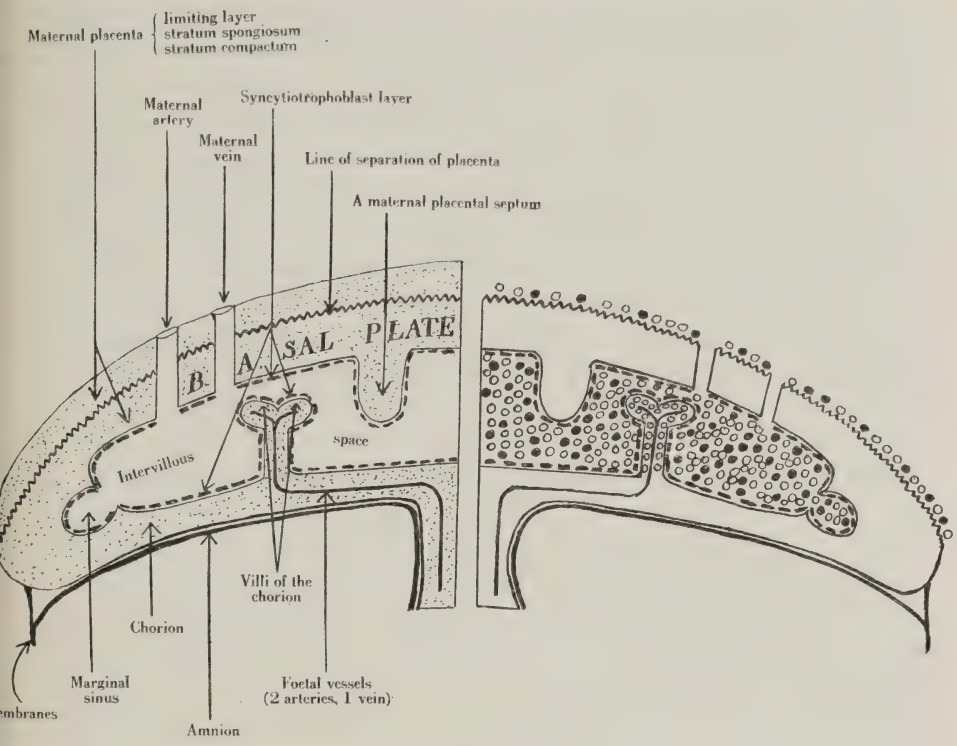


Fig. 1. Diagram of placental circulation (modified from Gray's anatomy). The left-hand figure represents the placenta before birth and the right-hand figure the same after birth. In the right-hand figure infected red cells are marked ● and uninfected red cells marked ○.

cells were found. The methods used were applied not only to the central portions of the placenta but also to the margin, and were :—

(1) The maternal surface of the placenta was carefully washed with normal saline solution ; smears were made from the surface, and also from blood obtained by scraping very lightly with a razor blade ; finally the thinnest possible slice of tissue was taken from the surface and from this thin slice films were spread.

(2) Films of blood from the placenta were examined at various depths from the maternal towards the foetal surface.

(3) The amnion was carefully washed with the normal saline solution and then reflected ; from the surface thus exposed smears were made and then, as in the case of the maternal surface, a thin portion of the tissue was snipped off and smears made from this thin portion.

(4) Wedge-shaped portions of tissue from the margin of the placenta and cylindrical portions from the centre were taken in such a way as to include both the maternal and foetal surfaces and the intervening tissue ; these were embedded and sectioned.

The examination showed that parasites were present in every preparation so made from infected placentas ; some variation occurred as shown in the attached table, in the proportion of infected erythrocytes present in blood films made at different parts of the placenta, from the tissue snipped from the maternal and foetal surface, and from the placental tissue at a point midway between these surfaces ; the results of such examinations are given in Table VI.

TABLE VI.

Showing percentage of erythrocytes infected at different parts and depths of the malarial placenta.

Blood films from	Edge of placenta	Centre of placenta
Tissue snipped from maternal surface ...	11·0	18·2
Tissue midway between maternal and foetal surfaces	9·8	36·2
Tissue snipped from foetal surface subjacent to amnion	8·2	9·4

As is seen in the table the centre of the placenta has a larger proportion of erythrocytes infected than the edge of the placenta ; further, the portion situated midway between the maternal and foetal surfaces in the central portion is the most heavily infected of all.

We were unable to account for this unequal distribution in any way except on the assumption that infected cells tend to accumulate here while uninfected cells pass on. If this area presented a more suitable medium in which the parasites could complete sporulation,

we might expect to find a greater proportion of sporulating forms of parasite in the infected cells of this area. We enumerated the sporulating forms found in each area with the result that in all areas the percentage of sporulating forms was found to be approximately the same ; for example, in one case where 200 parasites were counted in each area by each observer, the percentage of sporulating forms in each area was approximately 14.

Consideration of the distribution of parasites in relation to the anatomy of the placenta.

A point which early attracted our attention was that although the peripheral blood of the mother was free from parasites not only at the time of labour, but also in individual cases which were followed for a month after labour, yet parasites could be found on the maternal surface of the placenta in large numbers. In sections of the placenta thin walled sinuses are found near the maternal surface, some of which, presumably maternal arteries, are free from parasites, while others, presumably maternal veins, contain numerous parasites. Assuming that the condition found after the placenta is delivered were in existence before separation of the placenta, it is difficult to avoid the conclusion that parasites must be present in the maternal veins of the placenta in large numbers. Possibly this is so, and the failure to find these parasites in the peripheral blood may be due solely to the peripheral immunity which we have already postulated.

We believe, however, that the distribution of the parasites on the maternal surface of the placenta found after delivery may not represent the distribution as it occurs in the placenta before separation. The placenta is comparable to a flat sponge on one surface of which is the relatively thick covering membrane composed of chorion internally, and amnion externally, while on the other is the much thinner membrane composed of the remains of the stratum spongiosum externally and the basal plate internally ; internal to these is the lining of trophoblast. The intervillous space with the villi projecting into it occupies the whole area between the maternal and foetal internal surfaces.

The intervillous space everywhere extends up to the maternal surface, as well as to the foetal surface, at the margin as well as in the centre of the placenta. Consequently infected erythrocytes

contained in the intervillous space lie right against the maternal and foetal lining of syncytiotrophoblast. The processes given off into the space from the foetal surface, namely the chorionic villi, have a counterpart in the more scanty septal processes into the space from the maternal basal plate. All these processes are covered

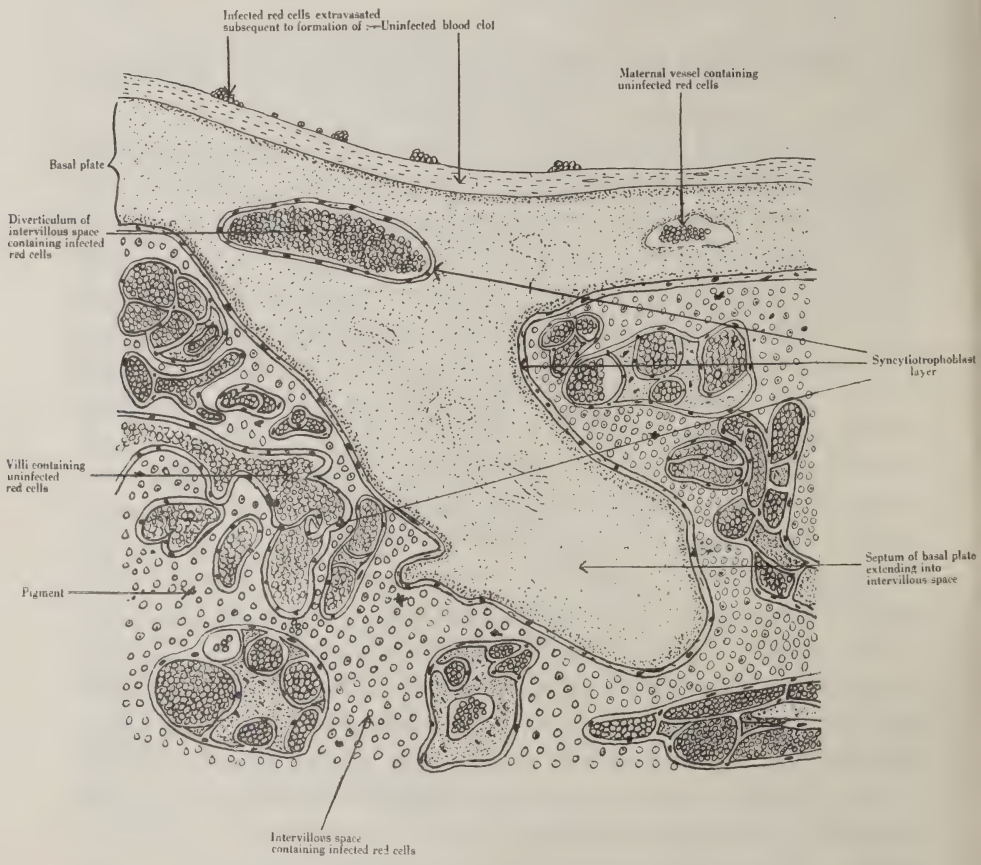


FIG. 2. Section through material surface of placenta [semidiagrammatic]. (Zeiss. Oc. 4. Obj. ½-inch.)

by syncytiotrophoblast and all are bathed in infected blood of the mother. At the origin of these processes are seen what at first appear to be areas of infected cells included in the chorion and basal plate. These are diverticula of the intervillous space cut across and are seen not only to contain infected erythrocytes

ERRATUM

Page 342, Fig. 2. For 'through material' read 'through maternal.'

but also to be lined by syncytiotrophoblast and in some cases to contain a portion of uninfected villous process.

This arrangement in itself would suffice to explain the fact that films made from even the thinnest slice of tissue from the maternal surface or from the foetal surface after reflection of the amnion contain numerous parasites. The presence of infected erythrocytes on the uncut maternal surface of the placenta as seen after its delivery is probably brought about therefore by the aid of two factors, both of which are dependent upon mechanical compression by the uterus upon the placenta after expulsion of the child and separation of the placenta has begun. If the cord has been tied on the maternal side the uterus is contracting upon a mass of tense villi, out of which the blood cannot be expressed through the cord. As the uterine contractions continue and increase, and as the vessels of the villi remain rigidly distended with blood, diminution in volume of the placenta takes place in two ways following the line of least resistance. In the first place the maternal blood lying in the intervillous space is forced back through the remnants of the maternal arteries and veins and emerges on the maternal surface of the placenta. On further pressure the intervillous space ruptures where the membrane is thinnest, that is, through the diverticula on the maternal side, and liberates on to the surface its contained parasites.

We are inclined to believe that in normal circumstances parasites do not extend beyond the limits of the syncytiotrophoblast layer which lines the intervillous space and which invests all processes into it, whether villi of the chorion or septa from the basal plate. Parasites, indeed, as we have shown, may always be found close to the maternal and foetal surfaces and often penetrate into both, but in the latter case they are normally lying in sinuous prolongations of the intervillous space and are still contained within the limiting syncytiotrophoblast layer. We have noted that parasites have never been seen by us in the villi themselves.

Rupture of the diverticula of the intervillous space appears to be attributable primarily to ligation of the cord on the placental side. If the placental side of the cord were not tied there might still be backward oozing from the maternal vessels, but it is clear that this leakage and the leakage consequent upon rupture of the intervillous space diverticula are very much accentuated by the fact that ligation

of the cord keeps the villi which comprise a large proportion of the total volume of the placenta not only engorged with blood but practically incompressible. In some cases it is possible to see in section that the villi themselves are ruptured although this is relatively rare;*

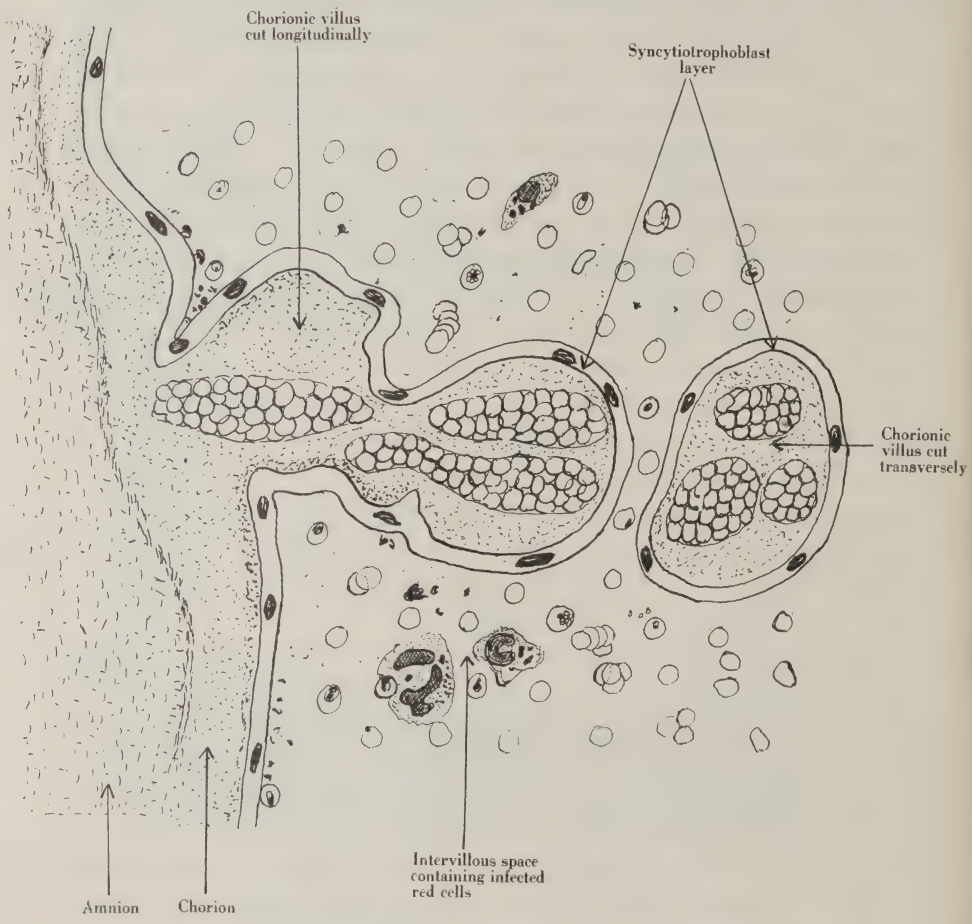


FIG. 3. Section through foetal surface of placenta, chorion and chorionic villi covered by syncytiotrophoblast layer [semidiagrammatic]. (Leitz. Oc. o. Obj. $\frac{1}{12}$. Draw tube down.)

separation and rupture of the syncytiotrophoblast layer over the villus has been observed occasionally and, still more rarely, escape of uninfected red blood cells from the villus.

* Since the above was written, one of us (R.M.G.), has had the opportunity of comparing the sections of malaria-infected placentas with sections of a large number of normal placentas at the Coombe Hospital, Dublin; this comparison showed clearly that the vessels in the villi of infected placentas are greatly dilated, in some cases to such an extent that the chorion, which normally forms the main bulk of the villus, is almost obliterated. Presumably such villi are more liable to rupture. This condition is well shown in several of the villi in Fig. 2.

If the cord were not tied it is conceivable that such rupture of villi might result in infection of the child via the cord vein ; but seeing that rupture is such a rare occurrence even when the cord is tied on the placental side, that is to say, when we have shown the conditions are most favourable to injury to the villi, it seems highly improbable that rupture of the villi could occur unless the cord is tied.

If the cord is tied on the child's side and then cut, leaving the maternal end free to bleed, it is extremely unlikely that any villi could be ruptured. In any case even if they did rupture the infection in these circumstances would obviously not affect the child via the cord. Even when the end of the cord is tied the risk of rupture of villi is extremely small, and here again the child is not exposed to risk via the cord.

There is one aspect of the question, however, which, although it is in the nature of a side issue from our investigation, appears to deserve mention. The facts here brought out have a distinct application to a controversy which has frequently arisen as to the merits or demerits of tying the placental end of the cord. The most recent exponent of the view that such ligation of the cord is injurious, is Vaughan (1925). The procedure is condemned on the ground that ligation of the cord places the uterus at a disadvantage in its efforts to contract.

We have had in this series of malaria infected placentas a unique opportunity of studying this question, and have had a method of distinguishing sharply between the foetal and maternal bloods from the circumstance that the maternal blood contained such a high proportion of infected erythrocytes in many of the cases. The information obtained by us by means of the study of malaria placentas in which the cord has been tied on the placental side enables us to bring forward new evidence to support that school which claims that the uterus when contracting on villi with cord tied is contracting on a mass which for all practical purposes is incompressible. We are, however, far from saying that we believe that this is injurious to the uterus, or that it has any deleterious effect upon its power of expelling the placenta, or upon its own final involution. These matters are outside the scope of this investigation, but we believe that what we have described may stimulate their study on the part of those whose special province it is to deal with pregnancy and the puerperium.

V. CRESCENTS

It has long been recognised that crescents appear relatively rarely in the peripheral blood of adult natives in endemic areas. Recently, Christophers (1924) has confirmed Schüffner's view that crescent formation is not associated with immunization, but that on the contrary, crescent formation is reduced during the process. The negative findings as regards crescents in the peripheral blood and placentas in this series would be in accordance with the idea that the majority of these cases were so far immunized as to prevent the appearance of parasites in the peripheral blood, and that all were so far immunized as to prevent the appearance of crescents either in the peripheral blood or in the placenta. It is of interest in this connection to note that Horowitz-Wlassowa (1924), while noting a specific antibody present in most cases of malaria, has failed to demonstrate its presence in those cases which show many schizonts or gametocytes in the cutaneous blood.

In writing of the peripheral blood of children in endemic areas, Christophers says ' Crescents here are therefore associated with the higher values of parasites, and hence one may judge with the period of acute infestation rather than with that of immune infestation.'

The absence of crescents in the placentas of the native women discussed is clearly not due to lack of parasite proliferation ; it may be that the placenta is in all cases a site in which for some reason crescent formation does not occur ; as suggested in our previous paper, this might be due to some intrinsic and yet unknown character of this organ which renders it unfavourable to the development of mature sexual forms. On the other hand, it is possible that the failure of crescents to develop in the placenta is an indication of a certain degree of immunity having been reached. If this is so, it would indicate that we have in the placental absence of crescents an early sign of the development of immunity. We are then faced with a complex arrangement ; the patient is infected with *P. falciparum ;* there exists a degree of immunity which prevents the development of crescents in the placenta as shown by direct examination of this organ, and probably in other organs as shown by the failure to find crescents in the peripheral blood ; this anti-crescent immunity, then, would appear to be of a general nature affecting the whole circulatory system. Quite a different picture is presented when we examine the immunity against asexual parasites. While the

peripheral circulation appears to be immune with regard to them the placental circulation, far from being immune, offers a most suitable soil for their development on an immense scale.

It is important, first of all, to decide whether the absence of crescent formation which has throughout our series characterised the placental blood is due to an inherent character of all placentas. This could be done by examining the placentas of women who, although infected with malaria, have not resided sufficiently long in an endemic area to acquire any degree of immunity. This investigation could be carried out readily in Europe in the case of pregnant women who return after a short first residence in an endemic area, and who are infected with malaria. If it should prove that such women readily develop crescents in the placenta, it would be necessary to examine also natives of endemic areas who had gone to Europe, and who had infection of the placenta. If the latter cases still showed no crescent formation in the placenta, it would be reasonable to draw two conclusions, firstly, that the absence of crescent formation in the placenta in this series was not due to an inherent character of the placenta, and secondly, that it was due to an acquired immunity. The value of such an examination lies in the fact that if it can be shown that acquired immunity is the cause of crescent non-production, we have in the placenta an accessible internal organ which possesses very obvious advantages for the study of malaria immunity. In view of the difficulty of obtaining material here for the purpose of this study in non-immunized persons, this part of the work must be undertaken elsewhere.

It is frequently stated that crescents are produced more readily after quinine administration. Several of our series of cases had received quinine before labour, some of them for as long a period as ten days, yet in no case, as we have shown, were crescents found.

VI. PATHOLOGICAL EFFECTS OF PLACENTAL INFECTION WITH *P. FALCIPARUM* ON MOTHER OR CHILD

Before discussing any effects which might be attributed to malaria infection, we give an account of the material and examination upon which our conclusions are based. In spite of increasing efforts to obtain permission to examine material post mortem, we have still a vast amount of prejudice to overcome ; this can only be done by gradual education and awakening the interest of those most nearly

concerned, namely, the natives themselves. Our records of post mortem examinations are consequently rather meagre.

The following are the material examined and the methods adopted ; in all cases Leishman's or Giemsa's stain was used.

1. *Maternal peripheral blood.* Thin and thick films were examined from the blood of the ear, at the time of labour.

2. *Placenta.* This was usually examined within 6 hours after labour ; exceptionally as much as 24 hours elapsed before examination was possible. The surface of the placenta was washed and cauterised ; an incision was made through the cauterised area and blood from the bottom of the incision was taken up in a pipette and used for spreading films.

3. *Umbilical cord.* The cord after being washed and cauterised was cut in two places, one as near as possible to the placenta and the other about six inches from the placenta ; films were spread from the blood in the vessels.

4. *Peripheral blood of living children.* Immediately after the birth of the child, thick and thin films were made from the peripheral blood.

5. *Partial examinations of cadaver of dead born children.* In most cases it was impossible to obtain permission for a complete examination ; puncture of certain of the organs by means of a needle was permitted in some cases, in addition to examination of the peripheral blood.

6. *Complete examination of cadaver of dead born children.* Where permission could be obtained, a complete examination was made. This comprised smears of peripheral blood, liver, spleen, kidneys, bone marrow, lungs and other organs.

7. *Examination of cadavers of children who died within seven days.* The examinations carried out in these cases were of the same kind as those in number 5 and 6.

Material from post mortem examination of the children was preserved and material from the placentas was fixed, embedded in paraffin and sectioned.

A. Effect on the mother before and after labour.

In Table VII given below, the main facts concerning the 55 infected mothers and their children are set out, with special reference to the fate of the child.

TABLE VII.

Showing clinical history and peripheral blood findings in 55 mothers infected in the placenta with *P. falciparum*; also the fate of their children.

Case No.	Age	Peripheral blood of mother	Temperature 3 days before or after delivery	Quinine, total amount given before delivery	Child born alive	Child lived 7 days
1	20	+	105° F.	25 gr.	Yes	Yes
3	24	o	100° F.	o	Yes	Yes
4	21	o	105° F.	o	Yes	Yes
5	35	+	100° F.	o	Yes	Yes
6	36	...	100° F.	o	Yes	No
9	18	+	N	o	Yes	Yes
13	18	o	105° F.	30 gr.	Yes	No
16	22	+	103° F.	36 gr.	Yes	Yes
17	36	...	103° F.	5 gr.	No	...
19	30	...	...	o	Yes	Yes
20	26	o	N	...	Yes	Yes
23	22	o	102° F.	o	Yes	Yes
34	37	o	...	...	Yes	Yes
35	22	o	...	...	Yes	Yes
38	20	o	...	...	Yes	Yes
45	36	o	N	o	Yes (2)	No (2)
51	21	o	100° F.	o	Yes	Yes

TABLE VII—*Continued*

Case No.	Age	Peripheral blood of mother	Temperature 3 days before or after delivery	Quinine, total amount given before delivery	Child born alive	Child lived 7 days
52	22	o	N	...	Yes (1) No (1)	Yes ...
53	15	o	N	o	Yes	Yes
58	28	o	100° F.	o	Yes	No
59	22	+	N	o	Yes	Yes
63	29	+	N	o	Yes	Yes
64	24	o	100° F.	o	Yes (1) Yes (1)	Yes (1) No (1)
67	26	o	N	o	Yes	Yes
69	24	o	N	o	Yes	Yes
71	24	+	N	o	Yes	No
75	25	o	N	o	Yes	Yes
81	23	o	100° F.	o	Yes	Yes
86	21	o	N	o	Yes	Yes
92	22	o	...	...	No	...
93	23	o	N	o	Yes	Yes
94	20	o	100° F.	o	Yes	Yes
95	32	o	N	o	No	...
96	36	+	...	o	Yes	Yes
98	20	o	N	50 gr.	Yes	Yes
101	24	...	N	o	Yes	Yes

TABLE VII—*Continued*

Case No.	Age	Peripheral blood of mother	Temperature 3 days before or after delivery	Quinine, total amount given before delivery	Child born alive	Child lived 7 days
102	26	o	N	o	No	...
103	28	o	N	o	Yes	Yes
108	26	o	101·5° F.	o	Yes	No
110	28	...	N	o	No	...
118	30	...	102·5° F.	o	Yes	Yes
128	28	o	N	o	Yes (1) Yes (1)	No (1) No (1)
134	16	o	N	o	Yes	No
136	17	o	103·8° F.	o	Yes	Yes
137	18	o	101° F.	o	Yes	Yes
138	33	o	101° F.	o	Yes	No
140	26	o	104° F.	o	Yes (1) No (1)	No ...
142	20	o	N	o	Yes	Yes
143	22	o	N	o	Yes	Yes
146	34	+	100° F.	o	Yes	Yes
147	26	o	N	30 grs.	Yes	Yes
150	24	o	103° F.	o	No	...
151	25	o	N	10 grs.	Yes	Yes
153	17	+	102° F.	15 grs.	Yes	Yes
155	21	o	...	...	No (1) No (1)	... ...

As is shown in the table 23, that is, nearly fifty per cent. of the infected mothers had fever, and three cases in which fever is not recorded received 50, 30 and 10 grains of quinine. It will be observed that in two cases in which both peripheral and placental blood was infected, namely, cases 59 and 71, there was no fever ; these cases are of special interest as each presented a massive infection of the placenta. It is important to note that certain cases in which malaria was suspected to exist received quinine in varying amounts for different periods before labour without the placenta being cleared of parasites.* Conversely there are seven cases not shown in this table which were diagnosed on clinical grounds as malaria and received quinine in varying doses, and in which the placenta did not contain parasites at the time of birth. Although we know that quinine in doses quoted has failed to eradicate parasites from the placenta in the cases mentioned in the table, we cannot therefore justifiably assume that similar doses will fail in all cases. Some or all of these seven cases, had they not been treated, might have proved infected by placental examination.

In view of the number of cases who received quinine before labour and who still had infection in the placenta, it is possible that the doses were administered too late in pregnancy and in too small quantity owing to the fact that these cases only enter hospital when labour is imminent. It is known (Forchheimer (1915)), that quinine administered to the mother is excreted in the urine of the child. There were three deaths among the 150 mothers of whom the placenta was examined. None of the three who died showed malaria either in placenta nor in the peripheral blood. With regard to the post-partum history of the mothers, we have practically no information, as these cases make a very brief stay in hospital, seldom more than a week. It is therefore not possible to state whether these cases have recrudescences of malaria after leaving hospital. So far we have not had any opportunity of examining the placenta of a woman who at her previous labour had been proved to have an infected placenta.

That infected red blood cells are left behind in the uterus in large numbers when the infected placenta is born there is no doubt, for

* Since the above was written, we have had the opportunity of observing a case whose peripheral blood showed malignant tertian parasites a week before labour, and who subsequently received quinine grains 20 for six consecutive days. The placenta of this case showed a few parasites and many pigmented leucocytes.

we have already shown that parasites abound on the maternal surface of the infected placenta when born. We have also observed parasites in the blood which escapes during delivery of the infected placenta. In the process of delivery of such infected placentas this may be a source of danger where such blood is permitted to reach abrasions on the skin of the child or the attendant.

We must assume that after the expulsion of the main bulk of the parasites with the placenta, one of two events happens ; either the remaining parasites are prevented from entering the maternal circulation owing to closure of the uterine vessels, and they are then thrown out with the remains of the stratum spongiosum, or they are absorbed into the maternal circulation. In the former event the mother's peripheral and general circulation does not become infected from the placental source as a direct result of labour ; in the latter event the result would depend on two factors, i.e., the dose of parasites absorbed, and the degree of the immunity which exists in the peripheral and general circulation of the mother.

B. Effect on the children.

1. *Before birth.* A total number of 164 children were born of the 155 mothers, this figure includes premature children. The single births numbered 146, giving 146 children, and the twin births numbered 9, giving 18 children ; two was the maximum number produced at one birth. There were 148 children born alive and 16 born dead. In the case of children born alive, the only means at our disposal for ascertaining the transmission of malaria parasites or their products to the child *in utero* was the examination of the child's cord and peripheral bloods.

Of the total 148 children born alive 4 are omitted from consideration here because the placentas relating to them were not received or were in such a state of decomposition that they could not be examined satisfactorily. Of the remaining 144 there were 51, i.e., 35·4 per cent. who were born of mothers whose placenta was infected ; while 93, i.e., 64·6 per cent. were born of mothers whose placenta was not infected. Only a short examination period after birth was possible, rarely more than 7 days, but a few cases were observed for a longer period. Of the 51 children born alive, of mothers with infected placentas, 13, i.e., 25·5 per cent. died within 7 days, the

remaining 38 survived the observation period ; of the 93 children born alive of mothers whose placenta was not infected, 5, i.e., 5·4 per cent. died within 7 days, the remaining 88 survived the observation period. Of 18 children born alive, and who died within 7 days, 13, i.e., 72·2 per, cent. were born of mothers whose placenta was infected, while 5, i.e., 27·8 per cent. were born of mothers whose placenta was not infected. Of the 16 born dead, 2 are omitted because the placentas relating to them were in such a state of decomposition that they could not be examined satisfactorily. Of the remaining 14 there were 10, i.e., 71·4 per cent. who were born of mothers whose placenta was infected* and 4, i.e., 28·6 per cent. who were born of mothers whose placenta was not infected.

In none of the children born alive were parasites found at birth, either in the cord or peripheral blood ; nor were pigmented leucocytes seen in any of them.

In 22 cases of dead children, i.e., some of the 10 children born dead, and some of the 18 cases who died within 7 days, we had additional means of diagnosis by post-mortem examination, a partial examination in 12 cases and a complete examination in 10 cases.

None of the 22 children who were examined by one or other of the above methods presented parasitic infection in the peripheral or cord bloods, nor in any organ examined ; nor were pigmented leucocytes found in the cord or peripheral blood of any of them. In three cases, however, pigment was found either free or contained in leucocytes in the internal organs of the child ; the mother's placenta in each of these three cases was infected with malaria. We are not in a position to state definitely what the source and nature of this pigment are ; while it may probably result from red cell destruction in the child, there is no direct evidence to show that this red cell destruction was brought about by the malaria parasite invading the red cells of the child. Our completely negative findings as regards parasites in any of the children are opposed to the idea that the pigment was produced by the parasite itself acting on the child's blood cells. We cannot exclude the possibility of infection having existed in the child and having died out before the time of examination at birth. It appears possible that toxins of malaria absorbed from

* The only case in our whole series in which infection of the placenta was diagnosed by the finding of pigmented leucocytes without parasites being present, is included in this group.

the focus of infection in the placenta will produce red cell changes in the child. In case 64 binovular twins were born with cords attached to adjacent placentas ; these placentas and cords presented remarkable differences in the blood as shown in Table VIII.

Table VIII

Showing the differences in the placentas, cords, and fate of the child in twins (both placentas infected).

	Placenta		Cord		Child	
	A	*B*	*A*	*B*	*A*	*B*
croscopic appearance of placenta, nd fate of child	Anaemic	Normal	Anaemic in first 6 inches only	Normal throughout	Died within 15 hours	Lived 7 days +
pe of parasite ...	30 % of parasites sporulating	No sporulating form seen	...	...	...	...
mber of parasites	1-15 fields	1-25 fields	...	...	...	...
croscopical ppearances	Evidence of great destruction of red cells	Normal except for infected red cells	Same as placenta for first 6 inches, remainder normal	Normal	Normal	Normal

The degree and stage of infection in the two placentas was different ; *A* having a higher degree of infection and a high proportion of sporulating forms. The uninfected red blood cells of placenta *A* presented all stages of lysis ; poikilocytosis and anisocytosis were present. Cabot's rings, pseudospirochaetes and fragmented red cells were very numerous ; on the other hand the uninfected cells of placenta *B* appeared normal.

In cord *A*, apart from the absence of parasites, the changes in the blood were identical with those seen in placenta *A* ; the changes noted were, however, confined to the first six inches of the cord nearest the placenta ; beyond this point cord *A* appeared normal ; cord *B* was normal throughout its length. The peripheral blood of both children appeared to be normal in so far as the non-nucleated red

cells were concerned, and a differential count of the leucocytes, and a comparison of the nucleated red cells showed the following results.

Peripheral Blood Diff. Leuc. Count	P.	LM.	SM.	Eos.	Bas.	Nuc. Red.
Twin *A*	39·0	8·5	40·0	1·5	...	11·0
Twin *B*	51·5	13·0	22·5	4·0	0·5	8·5

The different appearances of the blood in placentas *A* and *B* are illustrated in figures 3 and 4 in the Plate. This case is of interest in that whereas no parasites were found in the child and cord *A*, yet there was evidence in the cord blood of extensive damage to red cells similar to the damage in the placenta *A* blood.

We are compelled to leave unanswered the question what exactly is the pigment found in the organs of the child, in the cases referred to. It is suggestive, however, that in three cases in which pigment was found in the organs of the child, in each case it had died *in utero*, and that there were marked changes in the blood of the placenta belonging to each child; these changes resemble closely the appearances found in the placenta *A* and the first position of cord *A*; in case 64 no pigment was found. The remarkable appearance of the blood in a small portion of cord *A*, i.e., that nearest the placenta, and the similarity of the appearance in the blood of this part of the cord and that of the corresponding placenta suggest strongly that some agency acting in the placenta in causing destruction of red cells had also acted on the blood of the child in the portion nearest the placenta at the time the cord was tied. This agency we suggest is toxin liberated by the parasites sporulating in the placenta. If this child's cord had not been tied for some time after sporulation had occurred in the placenta, it is probable that all trace of this extensive localised destruction of red cells in the cord would have disappeared, being carried away by the circulating blood. The toxin which had in this case begun to pass into the child's blood stream was confined and prevented from circulating by the ligature of the cord, and so was acting in a concentrated form on a limited amount of blood with the results noted and illustrated. The toxic effects were

not observed in the blood of the cord at any point further away than six inches from the placenta.

In Table IX we give a summary of the salient facts concerning the children born dead or who died within 7 days, and in Table X which follows this, we give the figures which would represent the expected results in these cases if we assume that malaria had no part in the production of the mortality.

TABLE IX

Showing the number and percentage of children who were born dead or who died within 7 days, among 61 children born of 55 infected mothers and 97 children born of 95 uninfected mothers.

	Total	Born of 55 infected mothers		Born of 95 uninfected mothers	
		Number	Percentage	Number	Percentage
Children born dead	14	10	71·4	4	28·6
Children who died within 7 days ...	18	13	72·2	5	27·8
Totals	32	23	71·9	9	28·1

In Table X below are given the figures which would be expected provided that malaria infection had no influence.

TABLE X

Showing the totals and percentages in each group in Table IX redistributed in proportion corresponding to the ratio of the infected to the uninfected mothers, i.e., 55 infected to 95 uninfected in a total of 150 cases.

	Total	Born of 55 infected mothers		Born of 95 uninfected mothers	
		Number	Percentage	Number	Percentage
Children born dead	14	5·1	36·4	8·9	63·6
Children who died within 7 days ...	18	6·6	36·7	11·4	63·3
Totals	32	11·7	36·6	20·3	63·4

From a consideration of these two tables we can conclude, if such a small group can be taken as representative, that malaria here has a definite and important effect in the production of a high proportion of infant deaths *in utero* and in the first week of life.

It is difficult to say whether any isolated group of figures is representative of the true facts among a large population, but when it is remembered that these cases here discussed comprise the vast majority of all cases treated in the maternity hospital, and that they include members of every important tribe living in Freetown, we may legitimately assume that they form a fair sample of the urban population in this endemic area.

We believe that almost conclusive evidence is provided by the figures considered above ; but over and above this we have obtained from the study of a large number of infected and uninfected placentas data which convince us that the pathological alterations in the malaria-infected placenta are such that they cannot fail to have a deleterious effect on the child in one or more ways.

(1) *Congenital malaria.* In spite of the enormous infection seen in many placentas we have not seen any parasitic evidence of this condition. We are, therefore, in a position to repeat for this larger series of cases what we said in our previous account of our first 26 cases, namely, that this condition is of great rarity. In view of this it is interesting to note that in other countries very different results have been obtained ; for example, Ziemann (1924) records that Weselko, in 1922, in Albania attributed to congenital malaria the death in the first week of 144 children of mothers infected with *P. falciparum,* while Swellengrebel (1925) records 48 cases of congenital malaria in the near East in each of which a microscopical diagnosis was made at periods varying in time from 1 to 5 days after birth.

(2) *Interference with the nutrition of the child.* We have shown that in some cases as many as 65 per cent. of the red blood cells in the intervillous space are infected. It appears certain that in so far as the red cells are concerned in the nutrition of the child their function must be very seriously interfered with.

(3) *Toxic effects.* It is evident that large amounts of malaria toxins are being produced in heavily infected placentas. It is possible that the toxins produced by the malaria parasite are, as Ziemann (1924)

suggests, anchored in the maternal tissues, or they may be incapable of reaching the foetal circulation ; but the similarity of the blood changes observed in many infected placentas and in the placental portion of the cord in such instances as case 64 quoted above lead us to suppose that the toxins are at least in some cases capable of penetrating into the child's circulation. It appears probable from the above facts that definite effects on the child are brought about by the two last factors, that is to say, interference with nutrition and toxic absorption.

VII. THE AGE INCIDENCE OF MALARIA

(1) *Mothers.* The age incidence of 55 cases of malaria occurring among 148 mothers is shown in Table XI.

TABLE XI

Showing the distribution according to age of 148 maternity cases and of 55 placental malaria infections amongst them.

Years	Total maternity cases	Total malaria cases	Percentage infected
15-20	32	12	37·5
21-25	55	20	36·4
26-30	37	13	35·1
31-35	8	5	62·5
36-40	14	5	35·7
41-45	2	0	...
Totals	148	55	37·2

Excluding the 41-45 age period in which the figures are exceptionally small, the general effect of the table is to show that parturient women at all ages are equally susceptible to malaria infection in the placenta. Taking this table in conjunction with Table VII it will be observed, in so far as clinical manifestations of malaria and effect on the children are concerned, that there is no outstanding difference between the ages groups. It is surprising to observe that some very young mothers, age-group 15-20, e.g., case 53 age 15, and case 9

aged 18 in Table VII with placenta infected can not only pass through labour without clinical manifestations of malaria infection, but can also give birth to apparently perfectly normal children. That such tolerance exists only in some cases is, however, exemplified by case 13 aged 18, and case 153 aged 17.

(2) *In adult males and adult non-parturient females.* The figures we have in these groups have already been mentioned, i.e., adult males 150 and adult non-parturient females 43. As the total infection in these groups as judged by examination of the placental blood was only 2 per cent. and 7 per cent., respectively, a curve plotted from them would yield little information as regards the age incidence.

(3) *In children.* The peripheral blood of 158 children born of 150 mothers of whom 55 were infected in the placenta, and 95 were not so infected, proved negative as regards malaria at birth. In addition we have examined with negative results the peripheral blood of 41 new born children of 36 mothers ; the placentas of these mothers were not examined for malaria, but in 35 of them the peripheral blood was examined with the result that two were found positive, diagnosed by the finding of pigmented leucocytes. We were unable to follow the progress of these 199 hospital cases in order to ascertain when they would become infected. The only information to be derived from them in this connection is that at birth and for a period of a week or so after birth no infection was found in any of them. From an infant clinic, however, we are able to provide the figures already dealt with in Table II from which we can show the age distribution of malaria among 800 young children, namely a series of children of ages up to $2\frac{1}{2}$ years.* In each case of this series the peripheral blood was examined once. In Graph II is shown the distribution according to age of infected cases among these 800 children examined, the examinations extending over a period of a complete year.

It is seen that only one case is recorded as positive during the first month of life. From this time on to the age of $1\frac{1}{2}$ years the infection in children shows a regular rise. The character of this curve could be explained in either of two ways. It would be

* Nine children under $2\frac{1}{2}$ years who appeared in the total for seasonal incidence cannot be included here on account of uncertainty as to their exact age.

Page 360. For ‘examination of the placental blood’ read ‘examination of the peripheral blood.’